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Empagliflozin induced ketoacidosis in a patient presenting with new onset type 2 diabetes mellitus due to indolent pancreas cancer

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Empagliflozin-induced ketoacidosis in a patient presenting with new-onset type 2 diabetes mellitus due to indolent pancreatic cancer

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Key words: empagliflozin; euglycaemic diabetic ketoacidosis; pancreas cancer

Introduction

Sodium-glucose cotransporter 2 (SGLT2) is a protein located in the brush border of epithelial cells in the proximal tubule, which reabsorbs 90% of filtered glucose. Sodium-glucose cotransporter 2 inhibitors are a new class of oral medications for the treatment of type 2 diabetes mellitus (T2DM), which reduce plasma glucose levels by inhibiting the reabsorption of glucose from the proximal tubular epithelium. Sodium-glucose cotransporter 2 inhibitors are generally well tolerated, but this class of antidiabetic medications could be associated with serious adverse events, including euglycaemic diabetic ketoacidosis (euDKA), lower limb amputation, bone fracture, acute kidney injury, serious urinary tract infection, and venous thromboembolism [1]. Euglycaemic diabetic ketoacidosis is defined as DKA seen at a blood glucose level of less than 250 mg/dL. There are multiple mechanisms to explain the pathogenesis of euDKA in patients taking SGLT2 inhibitors, including hyperglucagonaemia, insulinopaenia, and overproduction of ketone bodies. Here, we report a patient with new-onset T2DM due to pancreatic cancer, who presented to the emergency room with euDKA on empagliflozin treatment. Furthermore, we performed a review of the literature previously reported SGLT2 inhibitor-associated euDKA.

Case presentation

A 58-year-old man presented to the emergency room with a one-day history of excessive thirst, slurred speech, and fever on October 23, 2019. Blood pressure was 90/60 mmHg, pulse rate was 124 beats/min, and body temperature was 38°C. The patient had no history of alcohol. On physical examination, oral mucosa was dry and skin turgor was moderately decreased. The initial laboratory findings are presented in Table 1.

Two weeks before the emergency admission the patient's medical history included impaired glucose tolerance, and he had a history of coronary artery disease for 10 years. He was on metformin twice daily. The patient was last seen by an endocrinologist with recent-onset T2DM 2 weeks before the emergency admission; haemoglobin A1c was 8.3%, and the level of C-peptide was 3.6 ng/mL at that time. Empagliflozin 10 mg once daily was added on October 7, 2019. The patient had been suffering from mild vague epigastric pain and 3 kg unintentional weight loss for the last six months. He was referred to a gastroenterology outpatient clinic. Magnetic resonance (MR) imaging of the abdomen was planned. Abdominal MR showed a solid mass 3.9 cm in diameter at uncinate process of the pancreas (Fig. 1). Biopsy of the pancreatic mass was consistent with poorly differentiated adenocarcinoma (Fig. 2). When the patient was seen at the oncology outpatient clinic for chemotherapy, he complained of excessive thirst, fever, and slurred speech. He had been taking empagliflozin for 14 days. The patient was diagnosed with euDKA. He was treated with IV insulin infusion, and IV hydration therapy. The C-reactive protein level was elevated. However, the chest X-ray was normal and there was no symptom of urinary tract infection, but the patient was treated with broad-spectrum antibiotics for a possible infection. Ketoacidosis resolved in 12 hours and a subcutaneous basal-bolus insulin regimen was initiated.

Figure 1. Abdominal T1-weighted MR scan showing solid mass 3.9 cm in size at the uncinate process

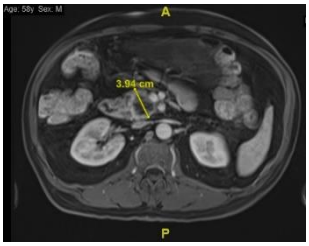
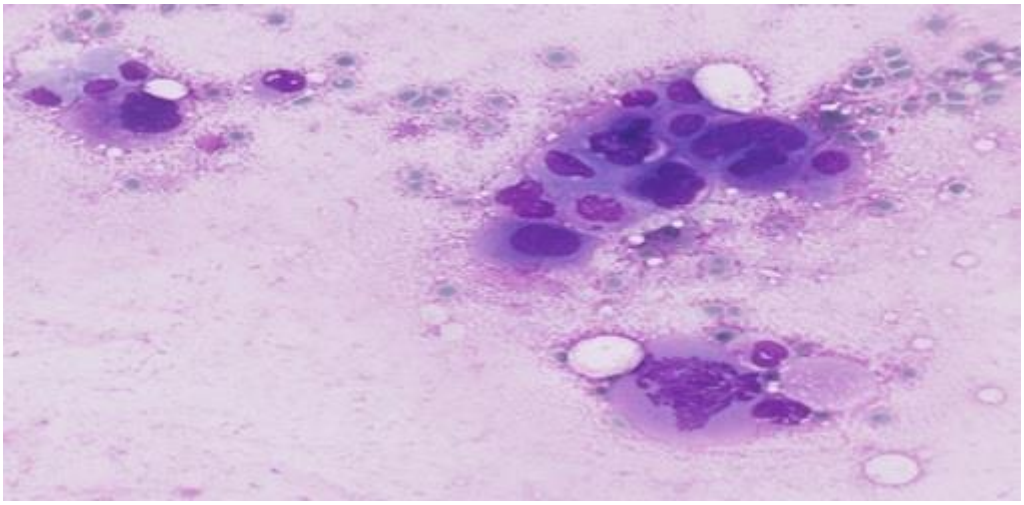


Figure 2. Poorly differentiated adenocarcinoma of the pancreas: cells have large pleomorphic nuclei



Discussion

The use of SGLT2 inhibitors is increasing, mostly driven by the results of cardiovascular outcome trials showing reductions in major adverse cardiovascular events, hospitalisation for heart failure, and progression of renal disease in people with T2DM [2]. Despite this positive news, concerns remain about some of the adverse effects of this group of drugs. Sodium-glucose cotransporter 2 inhibitors have recently been shown to induce euDKA. Risk factors for euDKA include latent autoimmune diabetes of adulthood (LADA), surgery, low carbohydrate diets, insulin withdrawal or dose reduction, chronic liver disease or heavy alcohol intake, and acute illness [3].

Our patient had negative anti-GAD and anti-ICA antibodies. We excluded LADA. Long-standing T2DM patients are at high risk of developing euDKA during SGLT2 inhibitor treatment [4]. Our patient's diabetes was new onset. This is the first case of empagliflozin-induced euDKA presenting with new-onset T2DM as an early sign of pancreatic cancer. Diabetic ketoacidosis as a first presentation of PAC is a rarely reported clinical condition [5]. It must be kept in mind that pancreatic cancer might be the precipitating factor for DKA in T2DM. Pancreatic cancer may have precipitated DKA through the factors that it secretes, which cause insulin resistance, or through causing insulinopaenia. In our case C-peptide level was normal, so insulinopaenia may not be the aetiology. In addition, prolonged fasting for the many

procedures such as radiological imaging, pancreas biopsy procedure, venous port catheterisation, and finally acute infection might have precipitated euDKA in our case.

Conclusion

In our patient, euDKA probably occurred due to empagliflozin. Empagliflozin had been started in the patient for its favourable cardiovascular effects. Our patient's diabetes was new onset. A point worth emphasising is that new-onset diabetes might be an early sign of pancreatic cancer. Malignancy may have increased the risk of euDKA when using SGLT2 inhibitor therapy. In particular, pancreatic cancer might have been a precipitating factor. Prolonged fasting for many procedures and acute infection might be the other underlying precipitating factors in our case. This group of drugs should be stopped especially if patients are going through a procedure that requires prolonged fasting. This is often a neglected issue that may precipitate euDKA.

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Table 1. Initial laboratory findings

Parameter (normal)	**Initial**
Arterial PH (7.36–7.44)	7.07
Serum bicarbonate (21–28 mmol/L)	2.7

Serum ketone (< 0.6 mmol/L)	3.5
Anion gap g (8–16 mmol/L)	29
Urine ketone (negative)	+++
Serum lactate (0.5–1.4 mmol/L)	1.4
Serum glucose (70–100 mg/dL)	206
Glycosuria (< 50 mg/dL)	2000
Serum sodium (135–145 mEq/L)	129
Serum potassium (3.5–5.0 mmol/L)	3.9
Chloride (98–107 mmol/L)	98.4
Serum creatinine (0.8–1.2 mg/dL)	1.0
Alanine transaminase (ALT) (< 35 U/L)	10
Aspartate transaminase (AST) (< 35 U/L)	12
Calcium (8.5–10.5 mg/dL)	9.6
C-reactive protein (CRP) (< 5 mg/L)	237
Procalcitonin (< 0.5 ng/mL)	36.4
Leucocytes (4.1–11.1 Ku/L)	17.33